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REGULAR RESEARCH ARTICLE

Predicting Antidepressant Effects of Ketamine: the Role of the Pregenual Anterior Cingulate Cortex as a Multimodal Neuroimaging Biomarker

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Abstract

Background: Growing evidence underscores the utility of ketamine as an effective and rapid-acting treatment option for major depressive disorder (MDD). However, clinical outcomes vary between patients. Predicting successful response may enable personalized treatment decisions and increase clinical efficacy.
Methods: We here explored the potential of pregenual anterior cingulate cortex (pgACC) activity to predict antidepressant effects of ketamine in relation to ketamine-induced changes in glutamatergic metabolism. Prior to a single i.v. infusion of ketamine, 24 patients with MDD underwent functional magnetic resonance imaging during an emotional picture-viewing task and magnetic resonance spectroscopy. Changes in depressive symptoms were evaluated using the Beck Depression Inventory measured 24 hours pre- and post-intervention. A subsample of 17 patients underwent a follow-up magnetic resonance spectroscopy scan.
Results: Antidepressant efficacy of ketamine was predicted by pgACC activity during emotional stimulation. In addition, pgACC activity was associated with glutamate increase 24 hours after the ketamine infusion, which was in turn related to better clinical outcome.
Conclusions: Our results add to the growing literature implicating a key role of the pgACC in mediating antidepressant effects and highlighting its potential as a multimodal neuroimaging biomarker of early treatment response to ketamine.

Keywords: pgACC, pregenual anterior cingulate cortex, multimodal neuroimaging biomarker, ketamine, antidepressant effects

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Significance Statement

A handful of studies have investigated the role of the pregenual anterior cingulate cortex (pgACC) in predicting the antidepressant effects of ketamine; however, they only explored single neuroimaging markers. We here report data from 24 major depressive disorder (MDD) patients who were investigated using both functional magnetic imaging (fMRI) during emotional processing and magnetic resonance spectroscopy (MRS) to explore the potential of pgACC activity to predict antidepressant effects of ketamine in relation to ketamine-induced changes in glutamatergic metabolism. Results show that antidepressant efficacy of ketamine was predicted by pgACC activity during emotional stimulation. In addition, pgACC activity was associated with glutamate increase 24 hours after ketamine infusion, which was in turn related to better clinical outcome. Taken together, we here provide first evidence, to our knowledge, that the pgACC can serve as a multimodal neuroimaging biomarker of early treatment response to ketamine in MDD patients.

Introduction

As the most common mental disorder with a lifetime prevalence between 15% and 20%, major depressive disorder (MDD) is the leading source of medical disability for people under the age of 45 in the developed world and has a major negative impact on public health and productivity. Even though standard antidepressant treatments are often effective, approximately 30% of patients suffering from MDD do not respond sufficiently to established pharmacological, psychotherapeutic, or somatic treatments (Bauer et al., 2013). Clearly, a better understanding of antidepressant treatment mechanisms and early prediction of response to a given treatment would help in selecting the most appropriate therapy for an individual patient and reduce the immense burden associated with depressive illness.

Among the most consistent findings in depression research are alterations of cerebral blood flow, glucose metabolism, resting state functional connectivity, and functional activation in the pregenual anterior cingulate cortex (pgACC), a region relevant for emotional processing and the establishment of mood states (Drevets et al., 2008; Pizzagalli, 2011). The pgACC is part of the default mode network (DMN; Raichle et al., 2001), and its aberrant activation with decreased negative BOLD responses (NBRs) during the performance of emotional tasks suggests depression-associated pathological abnormalities of the DMN regulate the processing of emotional material (Sheline et al., 2009; Grimm et al., 2011). Restored pgACC activity has been reported as a result of successful antidepressant drug treatment (Delaveau et al., 2011). Two meta-analyses and systematic reviews (Pizzagalli, 2011; Fu et al., 2013) as well as following studies (Godlewska et al., 2018a; Pizzagalli et al., 2018) highlight increased pgACC activity prior to treatment as a reliable biomarker of clinical response to a variety of antidepressant treatments, including pharmacotherapy, sleep deprivation, and repetitive transcranial magnetic stimulation (rTMS).

Increasing preclinical and clinical evidence underscores the role of glutamate (Glu) in the pathophysiology of depression and suggests that Glu modulation may induce rapid relief of depressive symptoms (Sanacora et al., 2012; Chadi G. Abdallah et al., 2015; Lener et al., 2017). Specifically, there is converging evidence for reduced concentrations of Glu and glutamine (Gln) in the pgACC (Walter et al., 2009; Luykx et al., 2012; Arnone et al., 2015; Shirayama et al., 2017; Wise et al., 2018; Benson et al., 2020). Because it is difficult to separate Glu clearly from its precursor and metabolite, Gln, the 2 compounds are often measured together as Glx, and, accordingly, Glx reductions have been reported in MDD (Yüksel and Öngür, 2010; Bond and Lim, 2014; Li et al., 2014; Godfrey et al., 2018; Moriguchi et al., 2019). Altered Glu levels in the pgACC might contribute to emotional dysregulation and perseverative rumination via failure of the greater ACC circuit to properly regulate emotional responses and facilitate task-based network switching (Johansen-Berg et al., 2008; Pizzagalli, 2011). Several studies have shown that decreased pgACC Glu and Glx content normalizes after successful antidepressant treatments, including electroconvulsive therapy antidepressants (Luborzewski et al., 2007; Yang et al., 2014). Thus, modulation of glutamatergic neurotransmission might represent a shared biological pathway among diverse antidepressant treatments (Skolnick, 1999).

A growing body of evidence suggests that the pgACC is also a key locus of action for ketamine, a promising Glu-modulating drug with a rapid antidepressant effect (for a review, see Alexander et al., 2021). Several lines of investigation have shown that ketamine increases prefrontal Glu levels through N-methyl-D-aspartate (NMDA) receptor inhibition and subsequent α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activation (Rowland et al., 2005; Stone et al., 2012; Zanos et al., 2016). Interestingly, the rapid antidepressant effect of ketamine might also be related to swift changes in task-related activity in the pgACC, as a study in healthy patients showed effects specifically during the processing of negative emotional stimuli 24 hours after ketamine administration (Lehmann et al., 2016). The importance of these ketamine-induced modulations is highlighted by studies suggesting that, similar to other antidepressant interventions, aberrant pgACC activity during emotional and cognitive processing prior to treatment identifies responders to ketamine (Salvadore et al., 2009, 2010).

This study therefore aimed to assess the potential role of the pgACC as a multimodal neuroimaging biomarker of early treatment response to ketamine using both functional MRI (fMRI) and magnetic resonance spectroscopy (MRS) in a sample of MDD patients. We hypothesized that increased pgACC activity (i.e., reduced NBRs) during emotional processing prior to treatment would predict antidepressant effects of ketamine 24 hours after the infusion. Further, we aimed to examine the relationship between neural activity and ketamine-evoked changes in Glu concentration in the pgACC.

METHODS

Participants

Data from 2 cohorts of patients suffering from MDD and treated with ketamine were included in the present study. The first was enrolled at the Department of Psychiatry and Psychotherapy, Charité-Universitätsmedizin Berlin (CHAR). The second cohort

was treated at the Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich (UZH). Major depression was diagnosed according to the criteria of the DSM-IV. There were no restrictions regarding antidepressant medication at the time of enrolment; however, medication intake was documented. Exclusion criteria were lifetime antidepressant treatment with ketamine; lifetime recreational use of ketamine; cardiovascular diseases such as hypertension, cardiac insufficiency, or myocardial infarct in the past 6 months; insufficiently treated anemia; hyper- or hypothyroidism; lifetime increased intracranial pressure or glaucoma; chronic physical diseases, in particular hepatorenal dysfunction; recent heart or head surgery; current pregnancy; as well as any relevant psychiatric or neurological comorbidity. Additional exclusion criteria regarding the scanning procedure were metallic body implants and claustrophobia. Participants gave their written informed consent before study entry. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Charité-Universitätsmedizin Berlin and the Ethics Committee Zurich.

Study Design and Ketamine Administration

All 24 MDD patients underwent fMRI and MRS prior to a single i.v. infusion of ketamine over 40 minutes administered by psychiatrists and anesthesiologists. According to clinical routine, patients treated at UZH received 0.25 mg/kg S-ketamine (Ketanest S, Pfizer, Zurich, Switzerland), and patients treated at CHAR received 0.5 mg/kg racemic ketamine (enantiomer ratio of 1:1). Because S-ketamine exerts a 3–4 times higher potency or receptor affinity than racemic ketamine, doses are typically reduced by 50% (Sinner and Graf, 2008; Hashimoto, 2019). For clinical assessment of depression severity at baseline, the Montgomery Asberg Depression Rating Scale was used at CHAR (Montgomery and Åsberg, 1979) and the Hamilton Depression Rating Scale at UZH (Hamilton, 1980). At both sites, treatment outcome was assessed by self-report of depressive symptoms using the Beck Depression Inventory (BDI) measured 24 hours pre- and post-intervention. A subsample of 17 patients underwent a follow-up MRS scan. The 24-hour follow-up time point was based on the observation that antidepressant effects of ketamine are most pronounced 1 day post administration (Zarate et al., 2006).

fMRI Paradigm

The fMRI paradigm was a passive viewing task consisting of 80 different photographs (40 positive and 40 negative) from the International Affective Picture System (IAPS) (Lang et al., 1997). Five pictures of the same valence composed a block of 20-second duration. To maintain participants' attention, a question was presented for 8 seconds after each block regarding the content of 1 of the 5 pictures (e.g., "Was there a red house in the picture?"). After the rating, a fixation cross was shown for 20 seconds. This allowed participants to recover from the previous emotional stimulation and served as a baseline condition. In total, the fMRI paradigm consisted of 16 blocks (8 positive and 8 negative) with an overall duration of 12.8 minutes. The experiment was presented via MRI-compatible video goggles (VisuaStim, Resonance Technology, Inc., Los Angeles, CA, USA) using Presentation software (Neurobehavioral Systems, Inc., Albany, CA, USA). Participants responded by pushing a fiber-optic light-sensitive key press.

Data Acquisition

Functional imaging and in vivo MRS measurements were performed on a Siemens Trio 3T (CHAR) and a Philips Achieva TX 3-T scanner (UZH) using a 32-channel head coil.

Functional images were acquired using T2-weighted standard echo planar imaging sequences. At CHAR data were collected with 37 oblique axial slices of 3 mm (TE = 30 milliseconds; field of view = 192 mm, 3 × 3 mm in-plane resolution, TR 2000 milliseconds, flip angle 70°) and at UZH with 32 contiguous axial slices of 4 mm (TE = 35 milliseconds; field of view = 220 mm, 2.75 × 2.75 mm in-plane resolution, TR = 2000 milliseconds, flip angle 82°, and sensitivity-encoded acceleration factor R = 2.0). At both scanning sites a 3-dimensional T1-weighted anatomical scan was obtained for structural reference.

For MRS, after a survey scan, at both sites a high-resolution T1-weighted gradient echo image ($1 \times 1 \times 1$ mm^3) was used for voxel planning and structural reference including tissue segmentation (CHAR: 176 slices, UZH: 160 slices). At CHAR, a single voxel spectroscopy sequence (TR = 3000 milliseconds, TE = 80 milliseconds, number of signal averages = 128, time = 6.5 minutes) was applied with PRESS localization scheme and voxel size of $35 \times 20 \times 25$ mm^3 (anterior-posterior [AP], right-left [RL], foot-head [FH]) (AP × RL × FH, 17.5 mL). At UZH, a maximum echo-sampled J-resolved PRESS protocol (as a 2-dimensional echo time series; Schulte et al., 2006; Fuchs et al., 2014) was set up to acquire spectra from a voxel with size of $32 \times 21 \times 24$ mm^3 (16.1 mL) in the pgACC (see Figure 1). A minimum echo time of 28 milliseconds and a repetition time of 1600 milliseconds were used. The echo increment to encode the indirect dimension was set to 2 milliseconds, and 100 steps were acquired with NSA = 8 per step (covering TE = [28:226], total NSA = 800, time = 24 minutes). An automatic projection-based second-order B0 shimming routine (Hock et al., 2013), without electrocardiogram triggering), outer volume suppression,n and VAPOR water suppression, was achieved (Tkac et al., 1999; Henning et al., 2009).

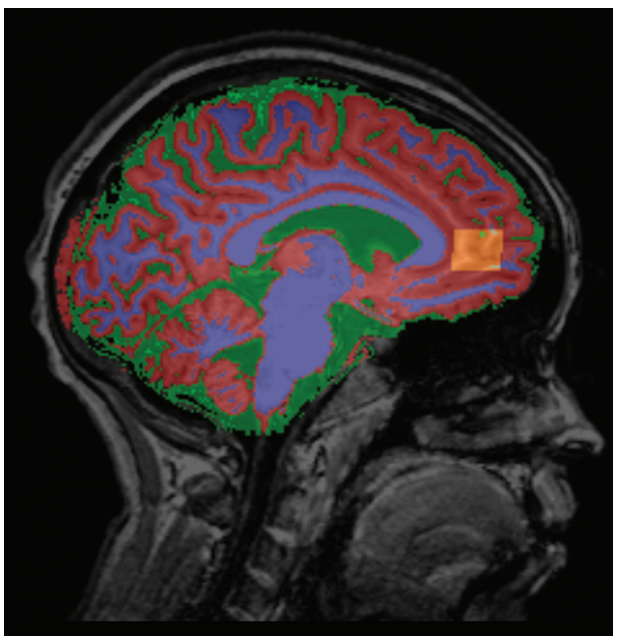

Figure 1. T1 weighted image of 1 exemplary patient. Color overlays represent segmentation results for grey matter (red), white matter (blue), and cerebrospinal fluid (green). In addition, the voxel placement is shown in yellow (figure created with MRIcron, Version 2.9.2019).

Data Analyses

Functional images were pre-processed using MATLAB 2020a (TheMathworks Inc., Natick, MA, USA) and SPM 12 (Statistical parametric mapping software, SPM; Wellcome Department of Imaging Neuroscience, London; UK; http://www.fil.ion.ucl.ac.uk). The data were registered to the mean, corrected for motion artifacts, mean-adjusted by proportional scaling, normalized into standard stereotactic space (template provided by the Montreal Neurological Institute), and spatially smoothed using a 6-mm FWHM Gaussian kernel. The time series were high-pass filtered to eliminate low-frequency components (filter width 128 s) and adjusted for systematic differences across trials. Single-subject analysis was performed by modeling the different conditions (positive picture viewing, negative picture viewing and fixation cross period) convolved with a hemodynamic response function as explanatory variables within the context of the general linear model on a voxel-by-voxel basis. Realignment parameters were included as additional regressors in the statistical model. Region of interest (ROI: x, y, z, in MNI space) analysis was performed to investigate NBRs in the pgACC. We built a spherical ROI (0, 42, 2) with a diameter of 10 mm based on our own previous studies (Grimm et al., 2012; Hartling et al., 2021). For the ROI analysis, contrast images of parameter estimates (emotional picture viewing vs baseline condition) were extracted for each participant separately using the REX toolbox (https://www.nitrc.org/projects/rex/).

MRS data were quantified with LCModel (Figure 2A; version 6.3-1M, CHAR; Provencher, 1993) and Profit2 (Figure 2B; UZH) using a basis set including Glu as 1 of the 21 (CHAR) and 18 (UZH) metabolites (Figure 3). Zero- and first-order phase correction and visual artifact inspection for ghosting, bad water suppression, and line shape distortions was conducted. Based on the high-resolution, 3-dimensional, T1-weighted images, the fractions of cerebrospinal fluid, grey matter, and white matter were calculated using SPM12 and a custom-written MATLAB script including functions from the GANNET framework (Edden et al., 2014). To account for partial volume effects and enable reliable quantification of Glu, the metabolite values were corrected for differences in the tissue volume composition (Gasparovic et al., 2006), including signal differences due to different TRs applied as described in Zoelch et al. (2017) to estimate the metabolite concentrations referenced to the internal water signal (both acquired with PRESS and J-resolved PRESS). As described previously, the absolute concentration estimation raises some difficulties such as the fact that T1 is

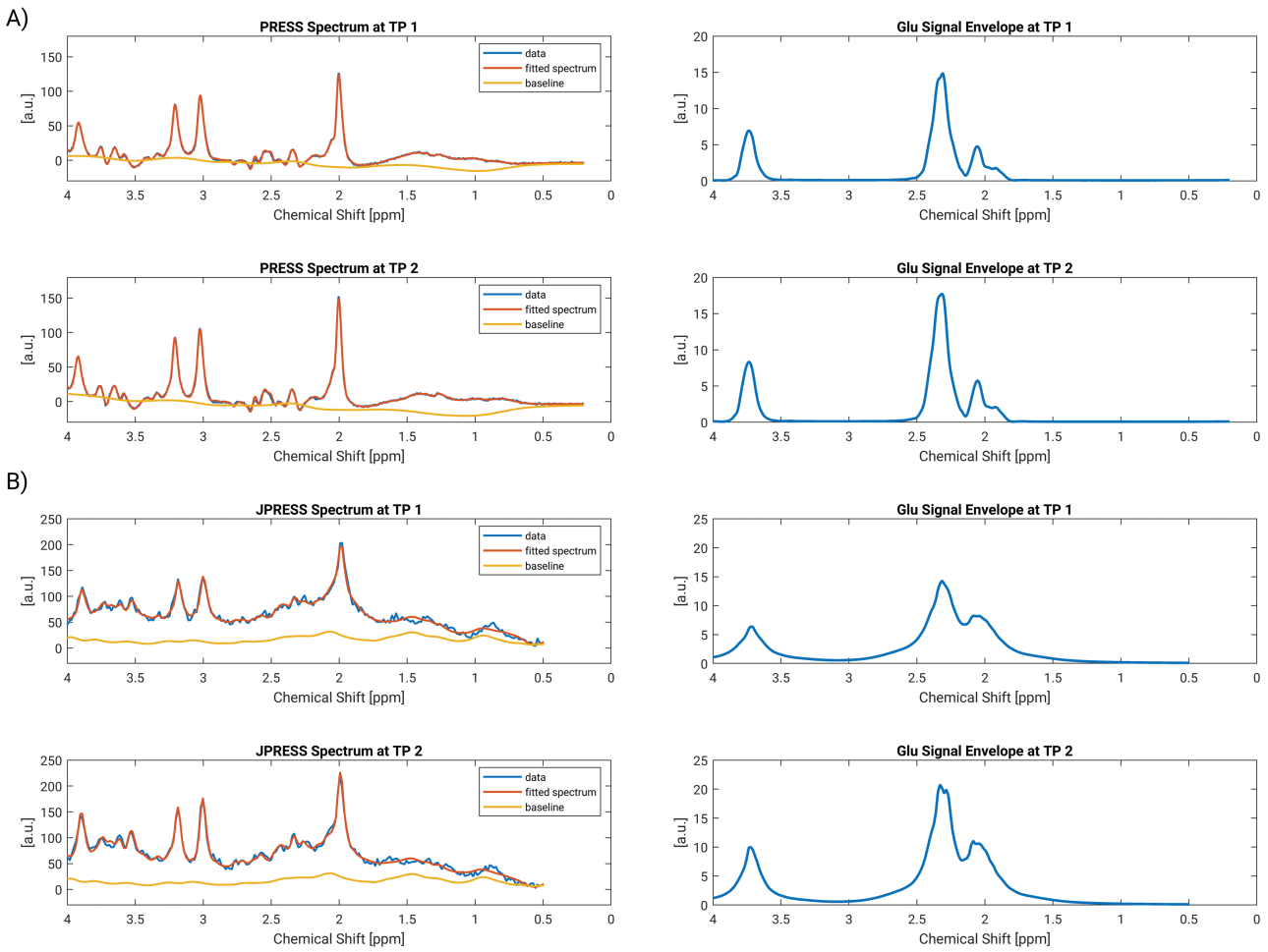

Figure 2. (A) Representative spectroscopy data with PRESS localization (TE = 80 milliseconds) and LCModel fitting for the first and second time point. (left): The measured data (blue), the fitted spectrum (red) and the baseline (orange) are shown. (right): The fitted signal contribution of glutamate (Glu) is shown as envelope for the first and second time point. (B) Representative 1-dimensional projections of the 2D JPRESS data and ProFit2 fitting for the first and second time point. Left: The measured data (blue), the fitted spectrum (red), and the baseline (orange) are shown for the first and second time point. Right: The 1-dimensional projection of the fitted signal contribution of Glu is shown as envelope for the first and second timepoint.

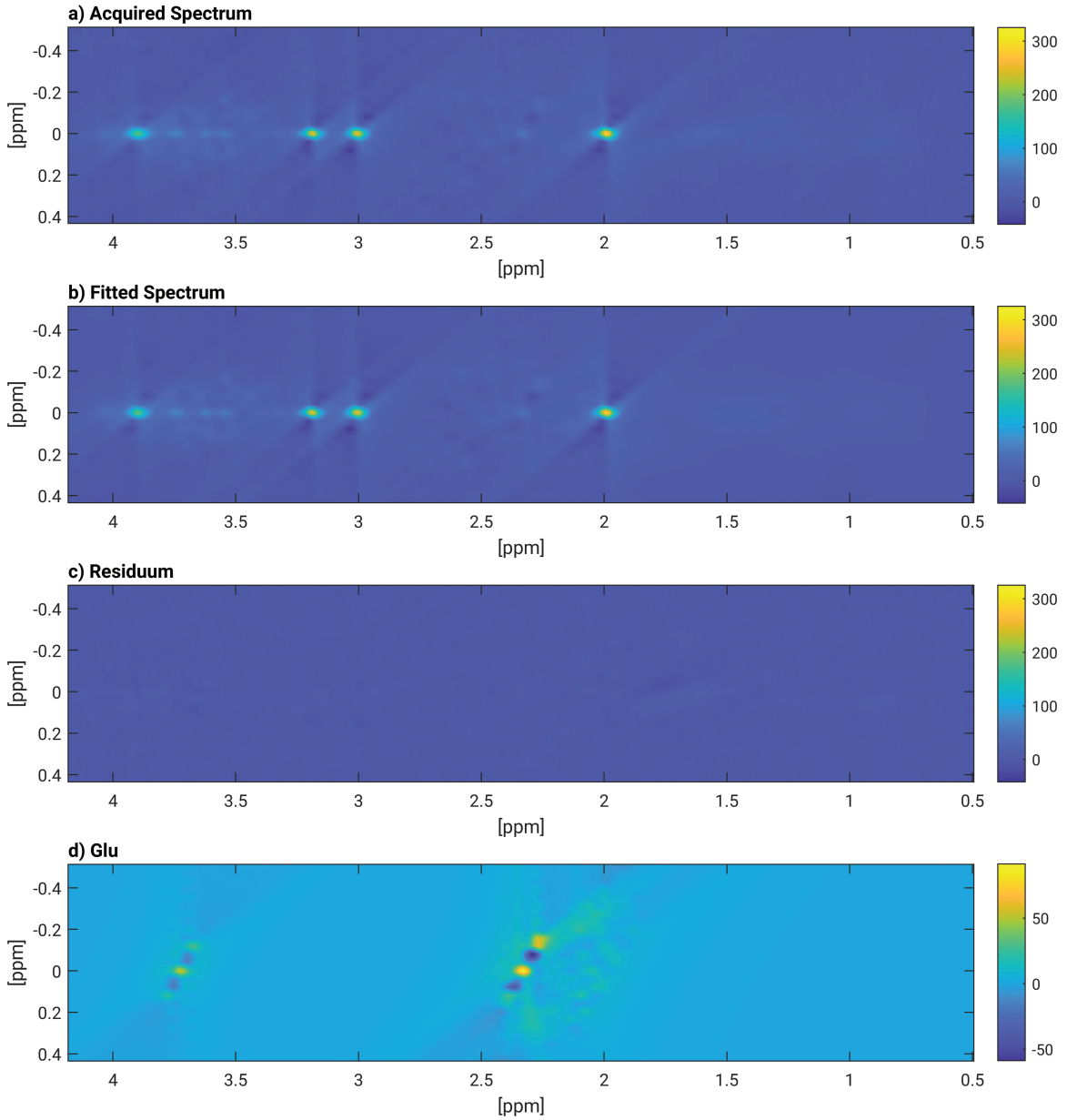

Figure 3. Representative 2-dimensional JPRESS data: the acquired spectrum (1), the fitted spectrum (2) and the fit error (residuum, 3) are shown including the signal contributions of glutamate (4).

not available for all metabolites in the basis set, and the absolute concentration is only known for creatine in grey and white matter. Therefore, we added an additional analysis showing simple metabolite over creatine ratios without correction for tissue composition and T1 relaxation time using just the T2-corrected values received from Profit2 (Zoelch et al., 2018). This allowed us to adjust the metabolite concentration for a different gray matter/white matter voxel ratio but also for different relaxation times (resulting in different metabolite signal from different echo times). All metabolite concentrations regardless of the Cramer–Rao lower bound (CRLB) value were included in the statistical analyses (no CRLB threshold was used; Kreis, 2016), with the exception of infinitely high CRLB values (in case a metabolite could not be fitted in a data set) to avoid bias toward higher concentrations. Of note, we did not use CRLBs to deselect measurements, because this might lead to the exclusion of lower concentration metabolites (Kreis, 2016). However, we can report that all Glu measurements in the ACC had CRLBs <7 (PRESS) and 6 (J-resolved PRESS).

Pearson's correlation analyses were conducted to determine whether pgACC activity prior to ketamine treatment predicted antidepressant effects and to explore the relationship between task-related fMRI signals, percent Glu change in the pgACC, and clinal outcome. Treatment outcome was calculated as percent BDI change. The 2-tailed threshold of significance was set at $P < .05$ unless otherwise noted. Analyses were carried out using SPSS Statistics (Version 25.0. IBM Corp.: Armonk, NY, USA).

RESULTS

Patient and Treatment Characteristics

In total, 24 patients diagnosed with MDD (14 females) with a mean age of 44.4 years (SD = 11.8; range = 25–64 years)

participated in the study. Fourteen patients were included at CHAR (mean Montgomery Asberg Depression Rating Scale score = 26.3; SD = 5.1), and 10 patients were included at UZH (mean Hamilton Depression Rating Scale score = 21.8; SD = 4.9). Overall, the mean BDI score at baseline was 34.1 (SD = 11.3) and significantly decreased to 24.7 (SD = 10.0) 24 hours after ketamine administration ($t_{(1,23)} = 4.1$, $P < .001$). A total 78% of the patients (18/24) showed a reduction of depressive symptoms. The mean clinical improvement was 22.6% (SD = 26.8%). There were no significant differences between patients at the 2 scanning sites (CHAR and UZH) with regard to age ($t_{(1,22)} = 0.77$; $P = .45$), sex distribution ($\chi^2_{(1,24)} = 0.02$; $P = .89$), or in their antidepressant response to ketamine as measured by the BDI % change ($t_{(1,22)} = 0.70$; $P = .50$). Current psychopharmacological medication (either as monotherapy or augmentation) included selective serotonin reuptake inhibitors (n = 7), serotonin and norepinephrine reuptake inhibitors (n = 7), tri-/tetracyclic antidepressants (n = 4), anticonvulsants (n = 3), atypical neuroleptics (n = 9), benzodiazepines (n = 6), and melatonin (n = 3). Details of patient characteristics can be found in the Supplement.

Predicting Clinical Improvement Based on Task-Related pgACC Activity

Patients showed an average NBR in the region of interest, the pgACC, during the presentation of emotional stimuli in the IAPS task. No significant difference in NBRs was found between positive and negative picture viewing ($t_{(1,22)} = 0.81$, $P = .43$); therefore, emotional conditions were merged for subsequent analyses.

In line with our hypothesis, we found that pgACC activity during emotional stimulation was a significant predictor of antidepressant outcome to ketamine ($r = 0.35$, $P_1 < .05$) (Figure 4). More specifically, increased pgACC activity (i.e., reduced NBRs) during the presentation of emotional stimuli in the IAPS task was associated with better clinical outcome 24 hours after the ketamine infusion.

Relationship Between Functional, Metabolic, and Clinical Parameters

In the subsample of 17 patients undergoing a follow-up MRS scan, we found a significant positive correlation between pgACC activity during the presentation of emotional stimuli in the IAPS task and Glu change in pgACC 24 hours after the ketamine infusion ($r = 0.42$, $P < .05$). Furthermore, Glu change in pgACC following ketamine administration was significantly associated with treatment outcome ($r = 0.65$, $P < .005$). More specifically, a stronger Glu increase was related to a better clinical outcome 24 hours after the ketamine infusion.

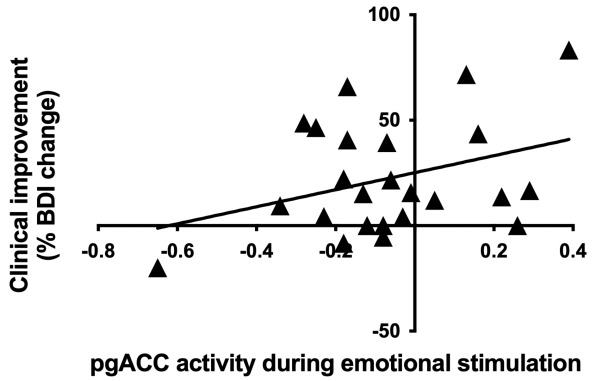

Figure 4. Prediction of clinical improvement (percent change in the Beck Depression Inventory [BDI] score) based on pregenual anterior cingulate cortex (pgACC) activity during emotional stimulation.

Discussion

In this study, we investigated whether the pgACC can serve as a multimodal neuroimaging biomarker of early treatment response to ketamine using both fMRI and MRS in a sample of MDD patients. We were able to show that task-related activity in the pgACC prior to ketamine administration can significantly predict antidepressant effects 24 hours later. Furthermore, pgACC activity during emotional processing prior to treatment was associated with Glu increase 24 hours after the ketamine infusion, which was in turn also related to better clinical outcome.

Our fMRI findings are in line with previous studies demonstrating an association of increased pgACC activity prior to treatment with positive antidepressant response across a variety of antidepressant treatments, neuroimaging modalities, and analytical approaches (Pizzagalli, 2011; Fu et al., 2013; Godlewska et al., 2018a; Pizzagalli et al., 2018). Based on these findings, the pgACC is currently the best supported candidate for a general neuroimaging biomarker for antidepressant response (Godlewska, 2020). Similarly, with regard to ketamine it was shown that pgACC activity during emotional and cognitive tasks predicted antidepressant response to ketamine (Salvadore et al., 2009, 2010). It has been proposed that the increased activity state of the pgACC may represent its treatment-responsive mode and be specifically important for clinical effects of rapid-acting glutamatergic drugs such as ketamine (Downey et al., 2016; Chadi G. Abdallah et al., 2017a; Godlewska, 2020). This hypothesis is supported by our finding of an association of pgACC activity with both symptom improvement and Glu increase 24 hours after the ketamine infusion. As the pgACC is part of the DMN (Raichle et al., 2001), it can further be suggested that its aberrant activation with decreased NBRs during emotional stimulation indicates that depressed patients, who are less able to disengage their DMN and actively engage with emotional stimuli, are more likely to response to ketamine treatment.

Our investigation of biomarkers across different modalities, that is, pgACC activity during emotional processing and Glu concentration, might thereby serve as a useful approach to optimize prediction of treatment response to ketamine. Although previous studies exploring single neuroimaging markers of antidepressant response to ketamine hold considerable promise (for a review, see Kadriu et al., 2020), multimodal technologies offer significant advantages but have previously mainly been used to better understand mechanisms of action underlying ketamine administration (Niciu et al., 2017; Evans et al., 2018; Nugent et al., 2019; Li et al., 2020; McMillan et al., 2020).

The role of Glu in the pathophysiology of depression as well as the rapid relief of depressive symptoms by Glu modulation have been demonstrated by preclinical and clinical studies (Sanacora et al., 2012; Chadi G. Abdallah et al., 2015; Lener et al., 2017). Depressive states are accompanied by glutamatergic system alterations such as decreased expression of NMDA and AMPA receptor subunits as well as decreased number of neurons (Rajkowska et al., 1999; Pittenger and Duman, 2008; Feyissa et al., 2009; Duman and Aghajanian, 2012; Yuen et al., 2012). While meta-analyses have generally reported diminished levels of Glu in depression (Luykx et al., 2012; Arnone et al., 2015; Moriguchi et al., 2019), data from individual studies are inconsistent and there are also reports of no differences or even increased Glu levels in MDD (Taylor et al., 2012; Chadi

G. Abdallah et al., 2017b; Li et al., 2017; Godlewska et al., 2018b). Accordingly, it has been discussed whether different profiles of glutamatergic dysregulation might be related to MDD severity or course, with high concentrations of Glu in the early illness phase being followed by lower levels as a result of neurotoxic effects on Glu neurotransmission (Portella et al., 2011; Arnone et al., 2015; Haroon et al., 2018; Hasler et al., 2019). Reduced concentrations of Glu in pgACC (Shirayama et al., 2017; Wise et al., 2018; Benson et al., 2020) might thereby eventually contribute to emotional dysregulation and perseverative rumination in MDD (Johansen-Berg et al., 2008; Pizzagalli, 2011). Indeed, Horn et al. (2010) found that only more severely depressed patients showed reduced Glu levels. Given that depression severity prior to ketamine treatment in the investigated sample here was comparable, our data support hypoglutamatergic function in depression and a ketamine- induced increase in Glu that subsequently triggers improvement of depressive symptoms. Decreased pgACC Glu content normalizes after diverse antidepressant treatments such as ECT, antidepressants, and rTMS (Pfleiderer et al., 2003; Luborzewski et al., 2007; Zhang et al., 2013; Yang et al., 2014; Njau et al., 2017) and might thereby represent a shared biological pathway (Skolnick, 1999). Our findings support the hypothesis that a perturbation of the Glu system in pgACC is critically implicated in MDD and treatment changes (Pizzagalli, 2011) and may be an essential mechanistic step in antidepressant response across treatment modalities. However, the timing of this perturbation may differ between treatments. Specifically, clinical response to ketamine may depend on a rapid change in pgACC Glu concentration. In contrast, treatment with antidepressants, ECT, and rTMS may have cumulative effects on the Glu system that are detectable weeks after initiation of treatment (Brennan et al., 2010).

Administration of ketamine has been found to result in a surge of Glu and increase in Glu/Gln cycling (Chowdhury et al., 2017), and previous 1H magnetic Resonance Spectroscopy (1H-MRS) investigations noted increased glutamatergic metabolite levels in healthy volunteers (Rowland et al., 2005; Stone et al., 2012) and increased Glx levels in MDD patients (Milak et al., 2016) following acute ketamine administration. Abdallah et al. (Abdallah et al., 2018) reported that ketamine increased prefrontal Glu-Gln cycling, thereby providing the most direct evidence in humans that ketamine increases Glu release in the prefrontal cortex, a mechanism implicated in the induction of rapid antidepressant effects. Milak et al. (Milak et al., 2016; Milak et al., 2020) found that Glu/Gln changes occur within the first 30–40 minutes postketamine administration in the pgACC, which supports the idea that the Glu burst happens quite early postketamine infusion (Javitt et al., 2018). Increased Glu concentration after ketamine has been linked to NMDA receptor inhibition and subsequent AMPA receptor activation (Rowland et al., 2005; Stone et al., 2012; Zanos et al., 2016). Interestingly, pgACC exhibits above average AMPA and below average NMDA receptor densities (compared with whole cingulate cortex) (Palomero-Gallagher et al., 2009) and regional variations of Glu concentration follow these receptor fingerprints (Dou et al., 2013). Accordingly, our result of a significant Glu response to a single subanesthetic dose of ketamine may be associated with the histoarchitectonical receptor fingerprint of the pgACC.

However, there are also investigations that found no effect significant changes in Glu concentration 1 hour postketamine infusion in healthy volunteers (Taylor et al., 2012), or 3 and 48 hours later in MDD patients (Valentine et al., 2011). Also, Evans et al. (2018) reported that ketamine did not affect Glu levels in the pgACC in MDD patients and that antidepressant response was not predicted by baseline Glu levels. Variations in voxel location, timing of the scan, imaging parameters, and sample size may explain these discrepant findings.

There are several limitations to this study. Our study sample was relatively small, and results will benefit from further replication in larger studies as well as in more homogenous samples of unmedicated patients. However, previous MRS studies investigating pgACC activity as a single neuroimaging biomarker of clinical response to ketamine included even smaller numbers of patients (n = 11, Salvadore et al., 2009; n = 15, Salvadore et al., 2010). Furthermore, considering the ongoing debate on antidepressant placebo outcomes (Holper, 2020), the lack of a placebo group in our study might imply that the reported pgACC activations predicted spontaneous improvement and are not directly linked to the effects of ketamine. However, this is unlikely, as previous work showed robust differences in clinical effects between ketamine and placebo (Berman et al., 2000). In addition, the current study was underpowered to assess the impact of psychopharmacological medication on neuroimaging data in our group of 24 depressed patients with heterogenous medication intake. As medication has been shown to influence many neuroimaging findings (e.g., Hafeman et al., 2012), higher-powered studies should control for and explore interactions with medication. Also, our primary aim was to link imaging biomarkers to symptom improvement after ketamine treatment, and we therefore argue that conclusions can be drawn from our analyses without a placebo condition. It should be considered that the reported data were obtained at 2 study sites and that the procedures at both sites were slightly different, with patients at UZH receiving S-ketamine and at CHAR racemic ketamine. Racemic ketamine is the mixture of the enantiomers R-ketamine and S-ketamine. However, consistent with our results, racemic ketamine and esketamine were shown to have similar antidepressant efficacy (Zanos et al., 2018). Another limitation is that we did not obtain MRS measures of Gln and GABA in the current study due to technical issues. Future studies should try to measure the concentrations of these additional metabolites in the pgACC to further investigate a possible relationship to antidepressant response.

In conclusion, our results not only provide insights into the relationship between pgACC activity, glutamatergic neurotransmission, and clinical outcome but support increasing evidence suggesting that the pgACC can serve as a biomarker to predict antidepressant effects across a variety of treatments. Particularly the combination of biomarkers across different modalities might optimize prediction of treatment response to ketamine.

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Author's Contributions

A.W. analyzed the data and wrote the manuscript; M.G. analyzed the data and wrote the manuscript; M.S. designed the study and acquired the data; P.W. analyzed the data; A.H. designed the study; E.S. designed the study; A.S. acquired and analyzed the data; A.H.M. acquired the data; M.B. designed the

study; S.A. designed the study and acquired the data; S.G. designed the study and wrote the manuscript. All authors revised and approved the final version of the manuscript.

Interest Statement

Malek Bajbouj was involved in a clinical trial by Johnson and Johnson investigating the antidepressant effects of ketamine. Simone Grimm has served as a consultant to and received research support from Boehringer Ingelheim Pharma.

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